i) at least one polymerizable macromer comprising at least one polyalkylene glycol (PAG) region having a first viscosity, and

ii) at least one PAG-interacting polymer (PIP) having a second viscosity, wherein the mixture has a viscosity greater than the sum of the first and the second viscosities;

A3

b) applying the solution to a surface of a substrate selected from the group consisting of cells, tissue surfaces and implants; and

c) polymerizing the solution to form a gel.

14. (Amended) The method of claim 9, wherein the macromer further comprises biodegradable regions.

A4

16. (New) The method of claim 15, wherein the gel is used to treat a detached retina.

17. (New) The method of claim 11, wherein the gel is used for the local delivery of the bioactive substance to a tissue.

A5

18. (New) The method of claim 17, wherein the tissue is a joint.

19. (New) The method of claim 15, wherein the gel is used to treat adhesion by application of the gel to a surface of a tissue.

20. (New) The method of claim 15, wherein the gel is used to treat adhesion by application of the gel to a surface of an implant.

REMARKS

As a threshold matter, Applicant thanks the Examiner for reviewing the IDS submitted on April 1, 2002. Applicants now submit a supplemental IDS listing documents cited by the International authority in the corresponding international patent application less than three months ago. Applicant kindly requests that the cited references be considered for this application.

Also, applicant submits herewith a request to correct the filing receipt and correspondence address and customer number in this application to reflect the Power of Attorney given to the undersigned by the inventors and submitted to the Patent Office on March 14, 2002. Applicants also submit a Supplemental Application Data Sheet bearing the corrected information.

Claims 1-20 are now pending in this application. Claims 1,4, 9, and 14 have been amended, and claims 16 to 20 have been added. Support for the claim amendments can

be found in the specification at least as follows: amendment to PAG macromers: at page 5, lines 1, 6, 11-16, and at page 6, lines 12-20, for example; amendment to description of viscosity of the mixture, at page 6, lines 22-26, from page 8, line 26 to page 9, line 22, in the Examples and the figures, for example; and amendment to biodegradable regions of the macromers: at page 5, line 24, page 9 line 29 to page 10 line 14 and the examples. Applicant believes that these amendments do not introduce new matter.

Support for the new claims can be found at least as follows: claim 16, at page 10, line 20; claim 17, at page 10, lines 18, 19, 25-29, and at page 11, lines 1-6; claim 18, at page 10, line 23; and claims 19 and 20, at page 10, line 20-22; and page 11, lines 7-13. Applicant believes that these new claims do not introduce new matter.

Rejection Of Claims Under 35 USC §112, Second Paragraph:

Claims 10, 12, and 13 are rejected as being indefinite in reciting PIP which has no antecedent in preceding claim 9 from which these claims depends. Applicant has amended claim 9, which now recites PIP as the abbreviation for PAG-interacting polymer.

Rejection Of Claims Under 35 USC §102:

Claims 1-4 are rejected over Balazs as being anticipated by Balazs's disclosure of mixtures of polyethylene oxide and hyaluronic acid. Applicant has amended the independent claim to now recite as one of the components of the mixture "a polymerizable macromer comprising at least a polyalkylene glycol region." Applicant respectfully submits that the amended claims are free of the cited prior art.

Balazs only discloses compositions of polyethylene oxide (PEO) and hyaluronate. In contrast Applicant claims compositions of a PAG-interacting polymer and a polymerizable macromer having at least one polyalkylene glycol region. Such polymerizable macromer differs from PEO in that it contains groups capable of polymerizing, while PEO is a stable, non-reactive polymer. Therefore, Applicant submits that Balazs does not anticipate the claims as amended. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

Claims 1-4 and 7 are rejected as allegedly being anticipated by Spiro. Applicant respectfully submits that Spiro does not anticipate the instant claims.

Applicant claims compositions of matter that are mixtures of at least two components, a macromer containing PAG and a PAG-interacting polymer. In contrast, Spiro teaches the formation of new chemical entities derived from the oxidation of hyaluronic acid (HA) and a sulfated polysaccharide (SP) and their subsequent reaction to a diamino-terminated polyethylene glycol to form a crosslinked material wherein the components are covalently bonded to each other. Because the components are covalently bonded, Spiro does not teach mixtures as claimed by applicants. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

Claims 1-15 are rejected as being allegedly obvious over the teachings of Sawhney in view of Balazs. Applicant respectfully submit that the amended claims are patentable over the cited combination of references as neither reference teaches the required motivation to combine the teachings of one with the teachings of other and Applicant demonstrated unexpected results.

Applicant submits that Sawhney does not teach or suggest compositions as presently claimed. The Examiner properly noted that, while Sawhney discloses PAG macromers, it does not teach PAG-interacting polymers. Sawhney does not suggest a need for increasing the viscosity of the macromer solutions, nor is Sawhney concerned in evaluating the viscoelastic properties of the macromeric solutions. Therefore Sawhney lacks the necessary motivation to combine its teaching with Balazs's to arrive at the presently claimed compositions.

As stated above, Applicant reiterates that Balazs also does not teach or suggest compositions as presently claimed. Balazs only studied the viscosity of mixtures of PEO and HA. It does not teach or suggest any modification to be made on the PEO to increase the viscosity of the mixtures. Yet Balazs does not show properties of compositions with other interacting polymers. Balazs also fails to cure the deficiencies of Sawhney in that it does not suggest modification of its mixtures to obtain desirable viscoelastic compositions such as behavior under shear desirable for implantable materials. Indeed, compositions of the present invention not only have an extremely high viscosity at low

shear rate, they also have a substantial decreased viscosity, by more than half, under high shear rate, permitting the compositions to be easily injected to the desired site of implantation by needle or catheter and yet regain viscosity at the site of implantation. Balazs is silent on this viscoelastic properties of its compositions; indeed Balazs only concerns cosmetic compositions for topical application wherein only viscosity is a relevant property. Therefore, Balazs does not provide the necessary motivation to combine its teaching with those of Sawhney to arrive at the presently claimed compositions.

Even when combined, Sawhney and Balazs do not teach or suggest the presently claimed compositions. Applicant submits that the claimed compositions present unexpected viscoelastic characteristics, which render the compositions more desirable for implantation. These viscoelastic properties could not have been foreseen even in view of the teachings of Balazs and Sawhney. In particular, these unexpected results can be clearly seen from a comparison (table below) of viscosity (η) in function of the shear rate plotted in Figure 2 (claimed composition) and Figure 6 (comparative data) corresponding to compositions prepared according to Examples 4 and 8 respectively.

	Shear Rate (RPM)					
Viscosity η (cP)	0.5	1	1.5	2	4	6
0.3% HA (2MDa)	160	145	(~130)	125	(<125)	(<125)
5% PEG (35KDa)	6	6	6	6	6	6
5% Macromer (20K TLA)	57	57	57	57	57	57
5% PEG + 0.3% HA	270	(~ 200)	190	(<190)	(<190)	(<190)
5% PEG + 0.3% HA	1.7	~1.4	~1.4	--	--	--
5% Macromer + 0.3% HA	~1050	~950	~850	~790	~600	~400
5% Macromer + 0.3% HA	6.5	6.5	6.5	6.3	--	--

Addition of HA to the solution of macromer increases the viscosity by a factor of 6 or more (see last row in table above), when in comparison the addition of HA to solution of PEG having a similar molecular weight (~35KDa) as the macromer (20KDa) the increase in viscosity is modestly one and half fold (see 5th row in table above). Thus

applicant has shown compositions that present an increase in viscosity four times higher (6/1.5) than the compositions similar to those of Balazs. This increase in viscosity is yet superior to the one observed by Balazs, as seen in Fig 2, which shows a less than three-fold increase in viscosity for a 2MDa PEG and .2% HA.

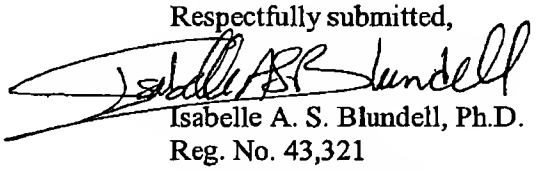
Surprisingly; this increase in viscosity for the composition of this invention is observed to be two times (6/3) higher than the one observed by Balazs, even though the molecular weight of the macromer (~20KDa) is about 100 times smaller than the PEO of Balazs (2MDa); whereas a lower rate of increase in viscosity is observed, i.e. one half lower (1.5/3) for small PEO (35KDa) compared to the large PEO (2MDa) of Balazs.

Therefore, the observed advantageous increase in viscosity in the composition of this invention is unexpected in view of the cited prior art. Accordingly, applicant submits that the claimed compositions and methods are unobvious over the cited prior art and are therefore patentable. Applicant respectfully request s that this rejection be withdrawn.

CONCLUSION

Applicant believes that all the issues raised in the Office Action have been addressed in conformity with the statutory requirements and thus places this application in condition for allowance.

Respectfully submitted,



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Appendix
Mark-up of Amended claims

1. A polymeric composition comprising a mixture of

a) at least one polymerizable [polyalkylene glycol (PAG) or PAG-based] macromer comprising at least one polyalkylene glycol (PAG) region having a first viscosity, and

b) at least one PAG-interacting polymer (PIP) having a second viscosity,

wherein [the PIP interacts with the PAG to produce a] the mixture has a [having a greater] viscosity greater than [either the GAG or PIP] the sum of the first and the second viscosities.

4. The composition of claim 1, wherein the [polyalkylene glycol or PAG-based] macromer [is selected from the group consisting of polyethylene glycol, copolymers of ethylene glycol with propylene glycol, and PAGs with crosslinkable groups] further comprises biodegradable regions.

9. A method for forming a biocompatible, flexible, bioadhesive gel comprising

a) forming an aqueous solution comprising a mixture of

i) at least one polymerizable [a polyalkylene glycol (PAG) or PAG-based] macromer comprising at least one polyalkylene glycol (PAG) region having a first viscosity, and

ii) at least one[a] PAG-interacting polymer (PIP) having a second viscosity,

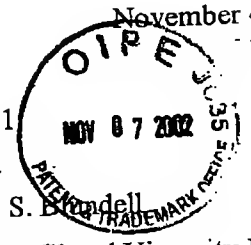
wherein the mixture has a viscosity greater than the sum of the first and the second viscosities [the PAG interacts with the PAG to increase the viscosity of the polymer solution];

b) applying the solution to a surface of a substrate selected from the group consisting of cells, tissue surfaces and implants; and

c) polymerizing the solution to form a gel.

14. The method of claim 9, wherein the [polyalkylene glycol or PAG-based] macromer [is selected from the group consisting of polyethylene glycol, copolymers of ethylene glycol with propylene glycol, and a PAG with crosslinkable groups] further comprises biodegradable regions.

November 4, 2002



Attorney Docket No.: 5181

Inventors: Avila et al.

Attorney: Isabelle A. S. Brundell

Title: Polyalkylene Glycol Viscosity-Enhancing Polymeric Formulations

Serial No.: 09/996,184

MAIL DATE CANCEL

The stamp of the Patent Office hereon acknowledges the receipt, on the date stamped, of a Certificate of First Class Mailing; a Fee transmittal with duplicate for Deposit Account (2 pages); Request for Extension of Time with duplicate for Deposit Account (2 pages); Reply with appendix (7 pages); Request for Corrected Filing Receipt (1 page); Marked-up Copy of Filing Receipt (1 page); Supplemental Application Data Sheet (3 pages); Supplemental Information Disclosure Statement Transmittal (1 page); Form 1449 (1 page); Copy of International Search Report (6 pages); 4 cited references and a Postcard.